The Role of the Frontal and Parietal Cortex in Proactive and Reactive Inhibitory Control: A Transcranial Direct Current Stimulation Study

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Abstract

■ Mounting evidence suggests that response inhibition involves both proactive and reactive inhibitory control, yet its underlying neural mechanisms remain elusive. In particular, the roles of the right inferior frontal gyrus (IFG) and inferior parietal lobe (IPL) in proactive and reactive inhibitory control are still under debate. This study aimed at examining the causal role of the right IFG and IPL in proactive and reactive inhibitory control, using transcranial direct current stimulation (tDCS) and the stop signal task. Twenty-two participants completed three sessions of the stop signal task, under anodal tDCS in the right IFG, the right IPL, or the primary visual cortex (VC; 1.5 mA for 15 min), respectively. The VC stimulation served as the active control condition. The tDCS effect for each condition was calculated as the difference between pre- and post-tDCS performance. Proactive control was indexed by the RT increase for go trials (or preparatory cost), and reactive control by the stop signal RT. Compared to the VC stimulation, anodal stimulation of the right IFG, but not that of the IPL, facilitated both proactive and reactive control. However, the facilitation of reactive control was not mediated by the facilitation of proactive control. Furthermore, tDCS did not affect the intraindividual variability in go RT. These results suggest a causal role of the right IFG, but not the right IPL, in both reactive and proactive inhibitory control. ■

INTRODUCTION

Response inhibition refers to the executive control ability to withhold ongoing decisions before execution (Logan & Cowan, 1984). Inhibitory control has been found to predict cognitive abilities and academic performance (Harnishfeger & Bjorklund, 1994). Impaired inhibitory control, on the other hand, is associated with mental health problems such as attention deficit hyperactivity disorder (ADHD) and drug addictions (Casey et al., 2011; Perez-Edgar et al., 2010). Therefore, understanding the underlying cognitive and neural mechanisms of inhibitory control is important for both educational and clinical purposes.

The stop signal task (SST) is one of the most widely used paradigms to study response inhibition (Logan, 1994; Logan, Cowan, & Davis, 1984). In this task, participants are instructed to respond to go trials and to inhibit their responses if, occasionally, a stop signal follows a go trial (i.e., turning it into a stop trial). It has been suggested that this task measures two types of response inhibition, that is, reactive inhibitory control that is cued by the stop signal and acts on the stop process and memory-related proactive inhibitory control that acts on the go process (Aron, 2011). Reactive inhibitory control is often indexed by the stop signal RT (SSRT), which measures the time needed to withhold the already initiated response. Individuals with better reactive inhibitory control ability can withhold their actions more quickly and thus have shorter SSRT (Duann, Ide, Luo, & Li, 2009; Aron & Poldrack, 2006; Aron, Monsell, Sahakian, & Robbins, 2004). In contrast, proactive inhibitory control is indexed by the preparatory cost (PC) or the increase of RT in go trials when the probability of stopping becomes higher (Verbruggen, Aron, Stevens, & Chambers, 2010; Chikazoe, Jimura, Hirose, et al., 2009; Vink et al., 2005). A higher PC indicates better proactive inhibitory control, whereas a higher SSRT indicates worse reactive inhibitory control. Previous research has found a negative correlation between these two indices, which suggests a positive relationship between proactive and reactive inhibitory control (Chikazoe, Jimura, Hirose, et al., 2009; Verbruggen & Logan, 2009; Vink et al., 2005). One interpretation of this positive relationship is that proactive inhibitory control in go trials may facilitate reactive inhibitory control in stop trials.

Neural imaging studies have revealed a distributed set of cortical and subcortical areas that are activated during inhibitory control tasks, including the frontal cortex, ACC, motor-related areas, posterior parietal cortex, and striatum (Aron, Robbins, & Poldrack, 2014; Aron, 2011; Congdon

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et al., 2010; Aron & Poldrack, 2006; Li, Huang, Constable, & Sinha, 2006). However, mixed results were reported about these regions' involvement in reactive and proactive inhibitory control. These controversies mainly focused on the function of the right inferior frontal gyrus (IFG) and the right inferior parietal lobule (IPL).

The right IFG has been primarily implicated in reactive inhibitory control. Many fMRI studies reported that the right IFG showed greater activation during the stop trials than during the go trials and that the BOLD signal change in the right IFG was negatively correlated with SSRT (van Belle, Vink, Durston, & Zandbelt, 2014; White et al., 2014; Congdon et al., 2010; Chikazoe, Jimura, Hirose, et al., 2009; Aron, Behrens, Smith, Frank, & Poldrack, 2007; Aron & Poldrack, 2006). A recent review of brain stimulation studies also supported this conclusion (Juan & Muggleton, 2012). Disruption of the right IFG function, either because of brain lesion or by TMS, increased the SSRT (Verbruggen et al., 2010; Chambers et al., 2006; Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003), whereas anodal transcranial direct current stimulation (tDCS) of the right IFG, which increased its function, reduced the SSRT (Ditye, Jacobson, Walsh, & Lavidor, 2012; Jacobson, Javitt, & Lavidor, 2011).

It remains inconclusive whether the right IFG is also involved in proactive inhibitory control (Aron, 2011). Although some studies using the SST emphasized the roles of the SMA, ACC, and striatum in proactive inhibitory control (Cunillera, Fuentemilla, Brignani, Cucurell, & Miniussi, 2014; White et al., 2014; Zandbelt, Bloemendaal, Neggers, Kahn, & Vink, 2013; Chevrier, Noseworthy, & Schachar, 2007; Vink et al., 2005), other fMRI studies and meta-analyses suggested that the right IFG was also involved in proactive inhibitory control (White et al., 2014; Swann et al., 2012; Jahfari, Stinear, Claffey, Verbruggen, & Aron, 2010; Chikazoe, Jimura, Hirose, et al., 2009). For example, the right IFG showed stronger activation for the uncertain-go trials (i.e., when it was not clear whether the trial was a go or a stop trial and proactive inhibitory control is involved) than in the certain-go trials (i.e., when there was no doubt that the trial was a go trial; Chikazoe, Jimura, Hirose, et al., 2009). Another study also found that the cues indicating more possible stop trials to come led to significantly slower responses and stronger right IFG activation compared to the cues indicating more possible go trials (Jahfari et al., 2010). Nevertheless, it remains to be determined whether the right IFG plays a causal role in proactive inhibitory control.

Although both the right IFG and the right IPL are parts of the ventral attention network (Corbetta & Shulman, 2002), the role of the right IPL in proactive or reactive inhibitory control has not been studied extensively, and the results are mixed. Some studies found stronger activations in the right IPL, including the angular gyrus (AG) and supramarginal gyrus, for stop trials than go trials in the SST (Hughes et al., 2014; Congdon et al., 2010; Aron & Poldrack, 2006) and for no-go trials than go trials in the go/no-go task (Menon, Adleman, White, Glover, & Reiss, 2001). In addition, greater activation in the right IPL was associated with shorter SSRT (White et al., 2014). However, stimulation of the right AG with TMS (Chambers et al., 2006) or anodal tDCS (Jacobson et al., 2011) did not change SSRT. Because neither of the above stimulation studies distinguished proactive and reactive inhibitory processes, the role of right IPL in response inhibition needs further examination.

The current study used tDCS to investigate the causal role of the right IFG and IPL in proactive and reactive inhibitory control in the SST. Reactive inhibitory control was indexed by SSRT, and proactive inhibitory control by the PC. We hypothesized that, compared to stimulation to the visual cortex (VC), anodal stimulation of the right IFG and right IPL would increase their excitability (Meinzer et al., 2012; Keeser et al., 2011) and facilitate the proactive and reactive inhibitory processes. The results of the current study should further our understanding of the neural mechanisms of response inhibition.

METHODS

Participants

Twenty-two neurologically healthy college students (10 women; 22.6 ± 3 years old) with normal or corrected-to-normal vision were recruited. All participants gave informed consent before their participation. The experimental and tDCS procedures were approved by the institutional review board of the State Key Laboratory of Cognitive Neuroscience and Learning at Beijing Normal University.

The SST

The SST (Logan, 1994) was used in this study (Figure 1A). This task consists of a number of go and stop trials. In go trials, an arrow pointing leftward or rightward was presented in the center of the screen, and participants were instructed to report the direction of the arrow as accurately and quickly as possible by pressing the left or right button within 1000 msec. In 25% of the trials (stop trials), a stop signal (i.e., a red circle) was presented shortly after the arrow was presented, and participants were instructed to withhold their response. The stop signal delay (SSD), that is, the interval between the onset of the arrow and the onset of the red arrow, was determined by a tracking procedure to ensure approximately 50% inhibition rate in all participants. Specifically, the SSD would increase by 50 msec (hence more difficult) when participants successfully inhibited their response and would decrease by 50 msec (hence easier) when they failed to stop. To reduce participants' anticipation, four step-up and step-down algorithms (staircases) starting with SSD values of 140, 180, 220, and 260 msec were employed to ensure the convergence to inhibition rate of 50% by the end of

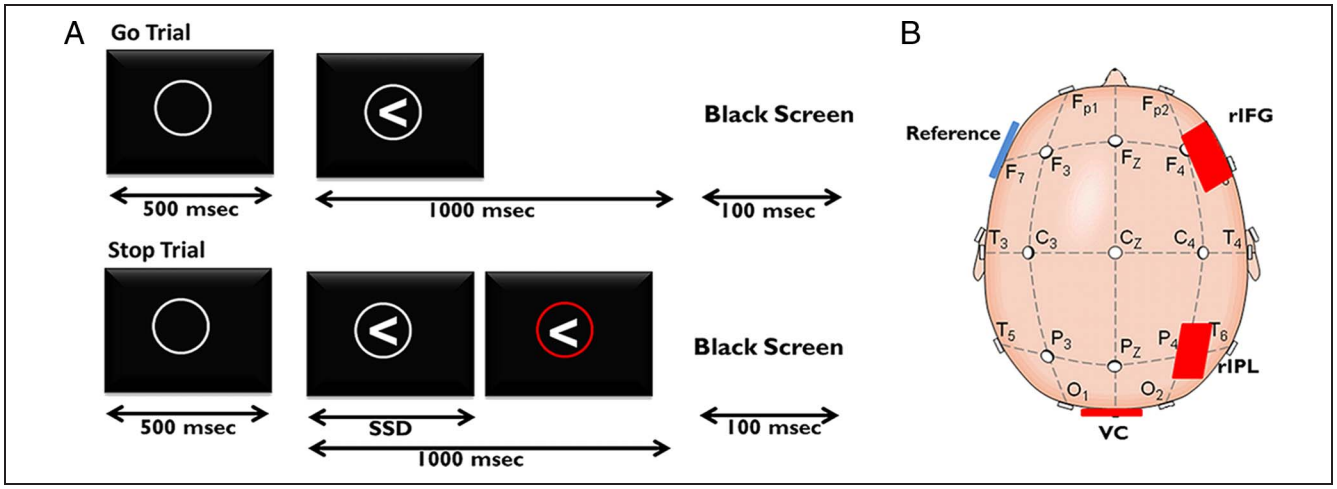

Figure 1. Experimental paradigm and the tDCS protocol. (A) The schematic of the SST. On the go trials, participants need to decide if the presented arrow faces right or left and press the corresponding button as accurately and quickly as possible. On the stop trials, a stop signal (the red circle) is presented after the onset of the arrow (the interval is indicated by SSD), and participants must withhold their response. (B) tDCS stimulations were conducted in right IFG (rIFG), right IPL (rIPL), and VC (red), according to the 10–20 electronic system; the reference was placed in the left cheek (blue).

the experiment. The staircases were independent but randomly interleaved (Xue, Aron, & Poldrack, 2008).

tDCS Procedure

A within-subject design was used in this study. Each participant completed the SST under three conditions. In the two experimental conditions, anodal tDCS was placed on either the right IFG or the right IPL. In the control condition, tDCS was conducted on the primary VC (Lu, Wang, Chen, & Xue, 2015; Xue, Juan, Chang, Lu, & Dong, 2012). The order of conditions was counterbalanced across participants. The three conditions were conducted over 5 days, with an intercondition interval of 48 hr. In each condition, the participants finished four blocks (64 trials each) both before and after tDCS. The tDCS effect was measured by the behavioral differences between pre- and post-tDCS stages.

tDCS was delivered with a DC-Stimulator (NeuroConn, Ilmenau, Germany), using a pair of electrodes housed in 5 × 5 cm saline-solution-soaked sponge coverings. The locations of the tDCS were determined by the international 10–20 EEG electrode placement system. The right IFG was located in the middle of F4 and F8 (Votinov, Aso, Koganemaru, Fukuyama, & Mima, 2013), the right IPL in P4 (Hsu, Tseng, Liang, Cheng, & Juan, 2014), and the VC in Oz (Lu et al., 2015; Xue et al., 2012). The reference electrode was placed on the left cheek (Figure 1B; Tseng et al., 2012; Xue et al., 2012). During tDCS stimulation, a direct current of 1.5 mA or 0.06 mA/cm^2 was applied for 15 min. The total charge in our current experiment was 0.054 C/cm^2. Both the direct current and the total charge were lower than the safety criteria of 25 mA/cm^2 for densities and 216 C/cm^2 for total charge (Nitsche, Liebetanz, et al., 2003). In addition, a 15-sec fade-in-and-fade-out design was added before and after stimulations to reduce the sensation caused by tDCS.

Behavioral Data Analysis

Stop signal data were analyzed based on the horse-race model (Logan & Cowan, 1984; Logan et al., 1984). First, mean SSD was calculated from SSD values for the last 128 trials of each stage, where the SSD was supposed to have converged. On rare occasions where the staircases did not converge, we removed the data from further analysis. In total, we removed two staircases from two participants. Following the procedure of White et al. (2014) and Band, van der Molen, and Logan (2003), we estimated SSRT using the quantile method to minimize the confound of estimation bias in individual differences in SSRT (White et al., 2014; Band et al., 2003). Specifically, all RTs in the correct go trials were arranged in ascending order, and the RT corresponding to the proportion of failed inhibition was selected as the quantile RT. SSRT was estimated by subtracting the mean SSD from this quantile RT.

To index proactive inhibitory control, previous studies have examined how the RT in go trials was modulated by the probability of an impending stop trial (Zandbelt, van Buuren, Kahn, & Vink, 2011; Chikazoe, Jimura, Hirose, et al., 2009). This modulation can be indexed by the PC (Chikazoe, Jimura, Hirose, et al., 2009) or the RT increase with increasing probability of an impending stop trial. In the current study, we calculated the PC by subtracting the mean RT of the first two post-stop go trials from that of the later post-stop go trials (all trials starting with the third post-stop go trial to the last trial before the next stop trial). Only correct go trials were included in this calculation.

One previous study suggested that inhibitory control might be related to intraindividual variability in go RT

(Bellgrove, Hester, & Garavan, 2004), which has been closely associated with the prefrontal function (Bellgrove et al., 2004; Stuss, Murphy, Binns, & Alexander, 2003; Stuss et al., 1999; Wilkins, Shallice, & McCarthy, 1987). For example, increased intraindividual variability has been often found in elderly participants and patients with dementia, head injury, ADHD, or schizophrenia (MacDonald, Nyberg, & Backman, 2006). Intraindividual variability was estimated by intraindividual coefficient of variation (ICV = go-RTsd / go-RTmean). A low ICV indicates less response variability (Bellgrove et al., 2004; Stuss et al., 2003). Because proactive inhibitory control is expected to increase the ICV, we calculated the ICV after regressing out the effect of the number of poststop trials on the go RT.

Repeated-measure ANOVA on the prestimulation SSRT, PC, and ICV revealed no significant effect of Stimulation condition (ps > .125), suggesting that there were no systematic biases in general cognitive state across the three conditions. The tDCS effect was measured as the difference between prestimulation and poststimulation performance in each condition. Location-specific effect was examined by one-way ANOVA, using Stimulation condition (right IFC vs. IPL vs. VC) as the within-subject factor.

Mediation Analysis

A targeted mediation analysis implemented in R (Tofighi & MacKinnon, 2011) was used to examine whether the tDCS effect on the SSRT was mediated by the PC. In this model, we included stimulation condition as the predictor (only the right IFG and VC conditions were included because the right IPL stimulation did not affect SSRT or PC), the SSRT change (from prestimulation to poststimulation stage) as the dependent variable, and the PC change as the mediator. We used the distribution-of-the-product method to compute confidence intervals, which has been proved to be more accurate than other methods when the sample size is small (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

RESULTS

Stop Rate and Go RT in the SST

We first calculated the stop rate in the last 128 trials, separately for each condition and stimulation stage. The mean stop rate was 47.70% (SD = 6.1%), which did not differ significantly from 50% (p = .121). A repeated-measure ANOVA using Stimulation condition and Stage (prestimulation vs. poststimulation) as within-subject factors showed no significant main effects or interaction (ps > .394). These results suggest that our tracking procedure successfully achieved approximately the target of 50% inhibition rate (Figure 2A).

A similar repeated measures on go RT showed a small, marginally significant decrease from prestimulation stage (402 ± 46.33 msec) to poststimulation stage (393 ± 46.7 msec; $F(1, 40) = 4.212$, $p = .053$), suggesting a subtle practice effect (Figure 2B). No other main effects or interaction were found (ps > .159).

Correlation between Measures in the SST

To examine the relationship between the go process, proactive and reactive inhibitory control, and intraindividual variability, correlations between mean go RT, PC, SSRT, and ICV were conducted for prestimulation and poststimulation data separately. For the prestimulation data, performance was averaged across the conditions. There was a significant negative correlation between the PC and the SSRT ($r = -.514$, $p = .014$; Figure 3A). No other correlations between mean go RT, SSRT, PC, and ICV were significant. For the poststimulation data, correlations were conducted separately for each condition. Results showed that the correlations between the PC and the SSRT were significant for all three conditions (ps < .024) and did not differ from one another based on Fisher's r-to-z test (ps > .194; Figure 3B–D). In other words, there appeared to be a stable positive relationship between proactive and reactive inhibitory control regardless of the location of tDCS. No other correlations were significant for poststimulation data (ps > .263).

Right IFG Stimulation Enhanced Reactive Inhibitory Control

One-way ANOVA on the SSRT change between prestimulation and poststimulation stages found a main effect of Stimulation condition ($F(2, 63) = 3.889$, $p = .026$). Post hoc least significant difference test found that the

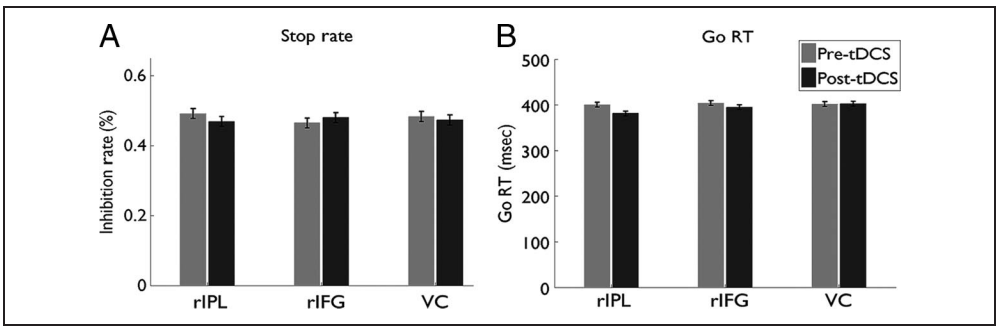

Figure 2. Stop rate (A) and go RT (B) were plotted as function of stimulation stage and stimulation condition. Error bars denote within-subject error.

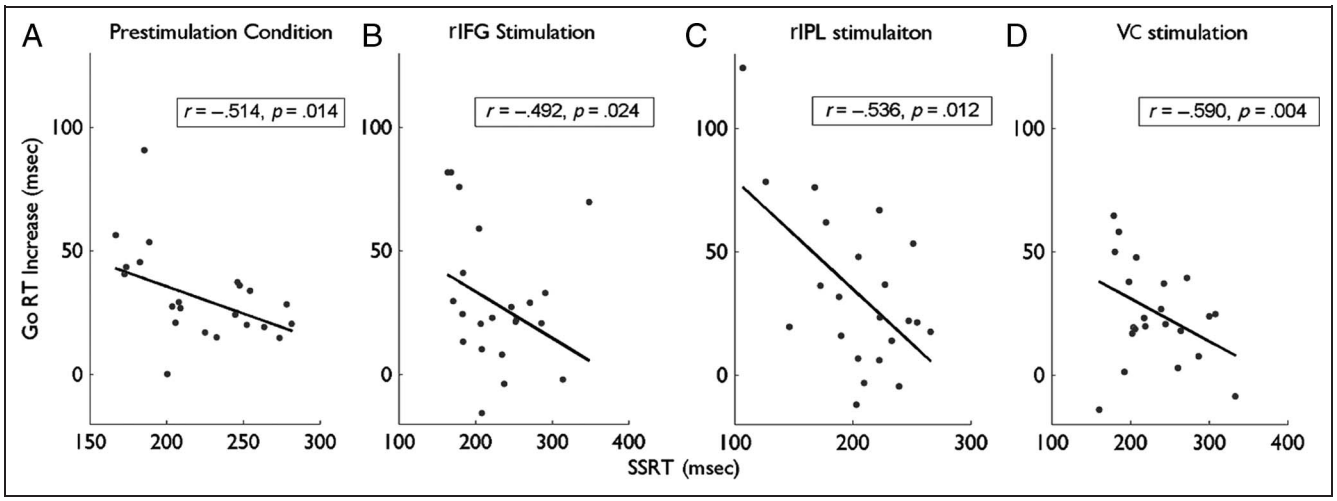

Figure 3. Correlation between PC and SSRT in the prestimulation condition (A) and the three poststimulation conditions (B–D).

SSRT showed a significantly greater reduction after right IFG stimulation than after VC stimulation ($t(21) = 2.916$, $p = .008$) and a marginally greater reduction after right IFG stimulation than after IPL stimulation ($t(21) = 1.881$, $p = .074$), but the SSRT change did not differ between right IPL and VC stimulations ($t(21) = 0.940, p = .358$; Figure 4).

Right IFG Stimulation Enhanced Proactive Inhibitory Control

The mean RT increased as the number of poststop trials increased ($F(3, 60) = 212.196$, $p < .0001$; Figure 5A), suggesting participants overall slowed down their response as the probability of a stop trial increased. One-way ANOVA on the change in the PC between prestimulation and poststimulation stages revealed a main effect of Stimulation condition ($F(2, 63) = 3.520$, $p = .035$). Post hoc least significant difference analysis showed a significantly larger PC as a result of right IFG stimulation compared to VC stimulation ($t(21) = 2.145$, $p = .044$) or IPL stimulation ($t(21) = 2.620$, $p = .016$). There was no significant difference between right IPL and VC stimulations ($t(21) = 0.435$, $p = .668$; Figure 5B).

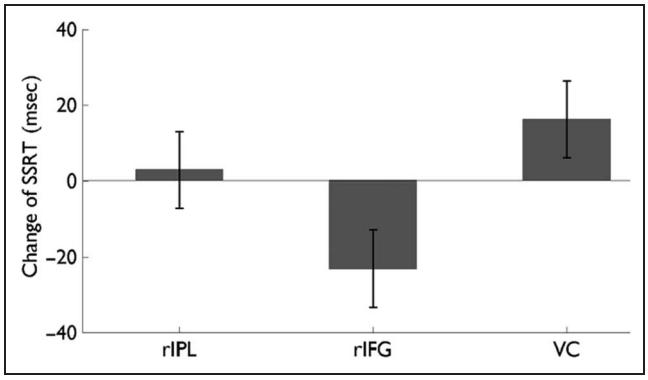

Figure 4. The effect of tDCS on SSRT change between pre- and post-tDCS. Error bars denote within-subject error.

Independent tDCS Effect on Proactive and Reactive Inhibitory Control

Because right IFG stimulation simultaneously decreased the SSRT and increased PC, leading to a positive correlation between proactive and reactive control, we conducted a mediation analysis to examine whether the tDCS effect on reactive control was mediated by proactive control. The results showed no significant mediation effect (product of coefficients = −9.547, $SE = 9.286$, 95% confidence interval [−30.664, 6.176]), and the direct effect of stimulation condition on the SSRT change was still significant after adding the mediator ($\beta = -29.44$, $SE = 11.03$, $p = .009$). These results suggested the tDCS effect on reactive inhibitory control was not mediated by facilitation of proactive inhibitory control.

tDCS Did Not Affect the Intraindividual Variability in Go RT

One-way ANOVA on the ICV change between prestimulation and poststimulation stages, using Stimulation condition as within-subject factor, showed no significant main effect ($F(2, 63) = 1.227$, $p = .30$; Figure 6), suggesting that anodal stimulation of right IFG and IPL did not affect the intraindividual variability.

The Performance-dependent tDCS Effect

Recent studies have suggested a performance-dependent tDCS effect, with generally stronger effects for participants with poorer task performance (Liang et al., 2014; Tseng et al., 2012). To examine this effect, we divided the participants into two groups ($n = 11$ for each group) based on their SSRT at the prestimulation stage across all

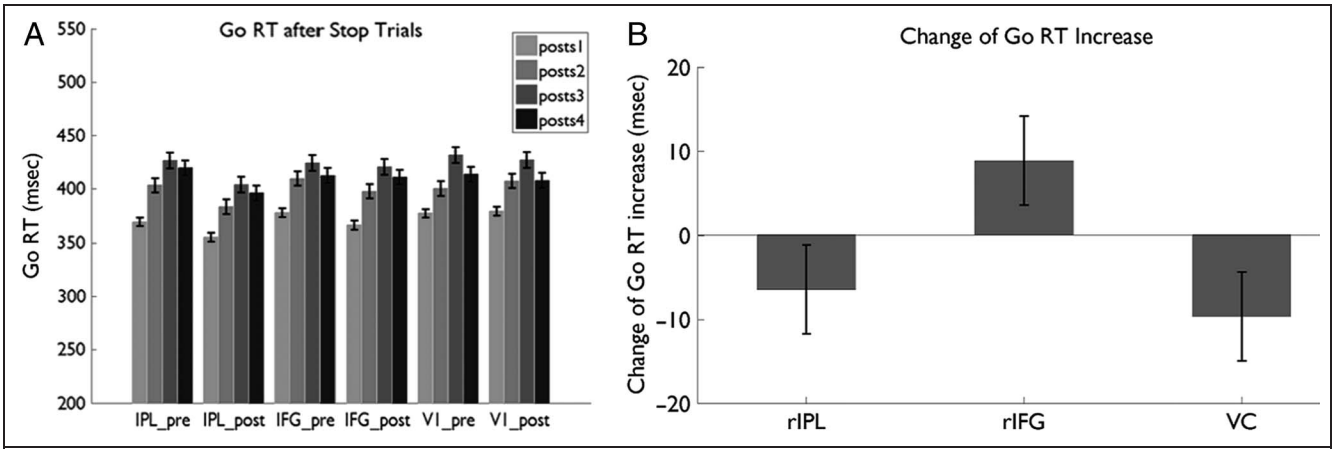

Figure 5. (A) The go RT increased as a function of the number of poststop trials. (B) tDCS effect on the PC change between pre- and post-tDCS stages. Error bars denote within-subject error.

three conditions. Although one-way ANOVA showed that right IFG tDCS significantly reduced the SSRT in the low-performance group ($F(2, 30) = 5.079, p = .013$) but not in the high-performance group ($F(2, 30) = 0.551, p = .582$), direct comparison of the two groups using mixed effects ANOVAs revealed no significant interaction between group and stimulation condition ($F(2, 40) = 0.62, p = .538$). Furthermore, no significant interaction was found for PC or ICV ($ps > .268$). These results thus did not provide strong support for the performance-dependent tDCS effect.

DISCUSSION

Using tDCS and the SST, this study examined the causal role of the right IFG and IPL in proactive and reactive inhibitory control. We found that anodal stimulation at the right IFG facilitated both reactive and proactive inhibitory control, but no effect was found after right IPL stimulation. These results provide causal evidence to support the role of the right IFG in both proactive and reactive inhibitory control.

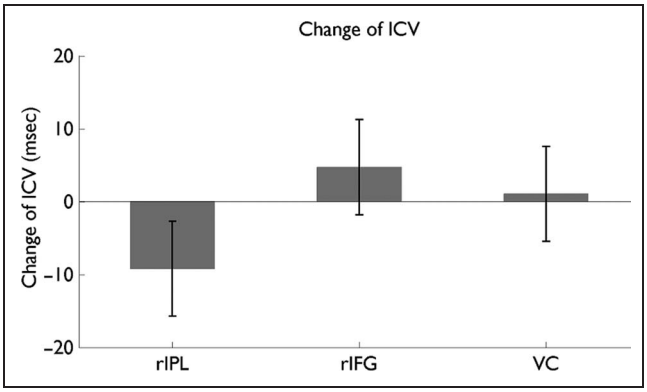

Figure 6. tDCS effect on the ICV change between pre- and post-tDCS stages. Error bars denote within-subject error.

Consistent with previous brain stimulation studies (Hsu et al., 2014; Juan & Muggleton, 2012; Jacobson et al., 2011; Chambers et al., 2006) and fMRI imaging studies (van Belle et al., 2014; White et al., 2014; Aron, 2011), we found that right IFG stimulation led to shorter SSRT in stop trials. In addition, this study provides the brain stimulation evidence for the right IFG's role in proactive inhibitory control, which is consistent with recent fMRI evidence (Thiebaut de Schotten et al., 2011; Jahfari et al., 2010; Chikazoe, Jimura, Hirose, et al., 2009) and the latest meta-analysis on a large set of fMRI studies using the SST (van Belle et al., 2014).

The current study further suggests that the tDCS effect on reactive inhibitory control was not mediated by the facilitation of proactive inhibitory control. Existing behavioral and imaging studies have shown that a stronger preparatory process may help to withhold the responses more quickly (Verbruggen & Logan, 2009) and reduce the inhibition-related neural activity (Chikazoe, Jimura, Hirose, et al., 2009). Consistently, we found a positive correlation between proactive and reactive inhibitory control. Nevertheless, there was no significant mediation effect of proactive inhibitory control on reactive inhibitory control, suggesting that right IFG tDCS could simultaneously facilitate both proactive and reactive inhibitory control.

Furthermore, we found that the ICV was not correlated with inhibitory control and that tDCS did not affect the ICV. This seems to be inconsistent with previous finding of the ICV's correlations with inhibitory control and activation in pFC (Bellgrove et al., 2004). One explanation of this inconsistency is the use of different inhibitory tasks, that is, the go/no-go versus the SST. Several lesion studies have also revealed increased ICV for patients with frontal lesion or psychiatric condition such as ADHD or schizophrenia (Stuss et al., 2003; Murtha, Cismaru, Waechter, & Chertkow, 2002; Janowsky, Shimamura, & Squire, 1989), but these studies often used different cognitive tasks such as a simple RT test and a source memory

task. Moreover, it is difficult for these lesion studies to precisely localize the deficits in specific prefrontal regions. Future studies should use functional imaging and a variety of cognitive tasks to examine the relationship between ICV, response inhibition, and prefrontal function.

Relevant to both proactive and reactive inhibitory control, the anodal tDCS on the right IFG has been shown to change its excitability and its functional connectivity with the pre-SMA (Cai, Cannistraci, Gore, & Leung, 2014; Aron, 2011; Aron & Poldrack, 2006), which is another important area implicated in both inhibitory control processes (Aron, 2011; Wardak, 2011; Chen, Scangos, & Stuphorn, 2010). For example, a diffusion tensor imaging study showed that the right IFG and pre-SMA were structurally connected (Aron et al., 2007) and the strength of this anatomical connectivity predicted performance on an inhibitory task (Buch, Mars, Boorman, & Rushworth, 2010). fMRI studies further suggested that functional connectivity between these two regions was increased during the SST (Duann et al., 2009). In addition, paired-pulse TMS on these two areas interrupted SSRT (Buch et al., 2010), and repetitive TMS simulation on the right IFG affected pre-SMA activation and impaired inhibitory control performance (Zandbelt, Bloemendaal, Hoogendam, Kahn, & Vink, 2012). Stimulation of the pre-SMA with tDCS also affected SSRT in previous studies (Hsu et al., 2011; Chen et al., 2010) and helped to withhold overt action errors, although it did not prevent the covert response impulses measured by EMG (Spieser, van den Wildenberg, Hasbroucq, Ridderinkhof, & Burle, 2015). Future stimulation studies should further examine the role of the pre-SMA in proactive inhibitory process.

We found that tDCS on the right IFG facilitated both proactive and reactive inhibitory control, suggesting that these two processes might share common neural substrates (Aron, 2011; Wardak, 2011; Chen et al., 2010). Nevertheless, based on existing functional imaging studies, some important cognitive and neural differences between proactive and reactive inhibitory control should be highlighted. First, these two types of inhibitory control are triggered by different information. Whereas reactive inhibitory control is cued by the stop signal, proactive inhibitory control is triggered by information stored in working memory (Aron, 2011). Indeed, it has been suggested that the right IFG could be involved in the detection of novel stimuli (i.e., stop signal; Erika-Florence, Leech, & Hampshire, 2014; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Sharp et al., 2010; Chikazoe, Jimura, Asari, et al., 2009) and right IFG stimulation could facilitate response inhibition by increasing the arousal and motivation. This is consistent with previous findings of the right IFG's role in the detection of changes in response contingency (Xue et al., 2013; Mullette-Gillman & Huettel, 2009).

More importantly, recent studies suggest that there were finer functional segregations within the right IFG region, such that the detection of a stop signal and the implementation of stopping may be supported by different subregions of the right IFG. For example, a TMS study found that, whereas the ventral–posterior part of the right IFG was involved in triggering the actual stop process, the dorsal–posterior part showed transient activity in correspondence to the occurrence of infrequent stop signals (Verbruggen et al., 2010). A recent meta-analysis suggests that, whereas the anterior insula is important for detecting behaviorally salient events, the right IFG is more involved in implementing inhibition (Cai, Ryali, Chen, Li, & Menon, 2014). Because of the limited spatial resolution of tDCS, the current study was not able to examine the finer functional dissociations of the right IFG and its adjacent areas in response inhibition. Future studies should use high-definition tDCS or TMS to further examine these issues.

Second, previous studies found that proactive and reactive inhibitory control showed different levels of specificity and involved different frontal BG connections (Aron, 2011). In particular, reactive inhibitory control seemed to have a "global" effect on corticomotor excitability (Cai, Oldenkamp, & Aron, 2012; Majid, Cai, George, Verbruggen, & Aron, 2012), whereas proactive inhibitory control was more selective (Majid, Cai, Corey-Bloom, & Aron, 2013). It has been suggested that reactive inhibitory control could be implemented via a hyperdirect pathway between the right IFG and the subthalamic nucleus (Aron et al., 2007), resulting in global inhibition (Majid et al., 2013). In contrast, the caudate might be more involved in proactive inhibitory control than in reactive control, resulting in more selective inhibition (Majid et al., 2013; Aron & Poldrack, 2006). How exactly tDCS stimulation at the right IFG produces differential behavioral and neural mechanisms for proactive and reactive inhibitory control deserves further study by combining it with functional imaging and EMG methods.

In contrast to the stimulation at the right IFG, right IPL stimulation had no effect on either reactive or proactive inhibitory control. Although right IPL activation was often reported during the SST (White et al., 2014; Congdon et al., 2010; Aron & Poldrack, 2006), its causal role has not been established. Our result is consistent with previous TMS or tDCS studies, which reported that stimulation of the right AG had no effect on SSRT (Jacobson et al., 2011; Chambers et al., 2006). The current study further suggests that right IPL stimulation did not change proactive inhibitory control as indexed by the PC. Thus, the functional relevance of parietal activations observed in previous imaging studies (Chambers et al., 2006; Garavan, Ross, & Stein, 1999) should be further examined.

Existing studies have suggested that the effect of tDCS is performance dependent, with a stronger effect for participants with a lower initial performance level (Hsu et al., 2014; Hughes et al., 2014; Jones & Berryhill, 2012). Our study did not provide strong support for this observation, probably because of the small sample size and narrow distribution of performance. Although the tDCS

effect for the SSRT was significant for participants with lower performance but not for those with higher performance, the interaction between performance level and stimulation condition was not significant. Furthermore, after tDCS, we did not find significant differences between the two performance groups. Future studies should further examine this issue with a larger sample size.

Both animal (Bikson et al., 2004) and human (Nitsche, Fricke, et al., 2003; Liebetanz, Nitsche, Tergau, & Paulus, 2002) studies found that anodal DC stimulation decreased the threshold for neuronal firing and increased the excitability of the cortical region and its functional connectivity with other brain regions (Meinzer et al., 2012; Keeser et al., 2011). Nevertheless, tDCS is a relatively crude method with low spatial specificity. There exist some computational models that can simulate the current flow in the brain (Brunoni et al., 2015; Woods, Bryant, Sacchetti, Gervits, & Hamilton, 2015; Kuo et al., 2013; Caparelli-Daquer et al., 2012; Dmochowski, Datta, Bikson, Su, & Parra, 2011), but they need to be verified with experimental methods. In addition, a combination of tDCS and functional imaging can help to better elucidate the neural mechanisms underlying the stimulation effect.

To conclude, this tDCS study clearly demonstrated that the right IFG, but not the right IPL, plays a critical role in both proactive and reactive inhibitory control. Future studies should combine functional imaging, EMG, and high-resolution brain stimulation techniques like high-definition tDCS or TMS to further examine the functional role of the right IFG's subregions in response inhibition and the neural mechanisms underlying the stimulation effect.

Acknowledgments

This work was sponsored by the National Natural Science Foundation of China (31130025), the 973 Program (2014CB846102), the 111 Project (B07008), and the NSFC project (31221003).

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